CHAPTER 17

Marine Algae: Natural Product Source for Gastrointestinal Cancer Treatment

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Contents

Abstract

Among marine organisms, marine algae are rich sources of structurally diverse bioactive compounds with various biological activities. In order to survive in a highly competitive environment, freshwater or marine algae have to develop defense strategies that result in a tremendous diversity of compounds from different metabolic pathways. Recently, their importance as a source of novel bioactive substances is growing rapidly and many reports have been published about isolated compounds from algae with biological activities. Many researchers reported anticancer activity of the compounds isolated from marine algae. Gastrointestinal tract cancer is one of the most frequent death causes of cancer in men and women. Especially stomach cancer and colon cancer are the second and third common cancer type in the world after lung cancer. Hence investigation of bioactive compounds against gastrointestinal cancer cells has recently become an important field for researchers.

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I. BACKGROUND

Around 70% of the earth's surface is covered by oceans and seas, and the organisms that learn to survive in this 70% has potential for biomass production. Algae survive in a large scale in the earth: in the sea, rivers, and lakes, on the land, or on other organisms. To survive in a competitive environment, freshwater and marine algae have developed defense strategies that result in a significant level of structural–chemical diversity, from different metabolic pathways (Barros *et al.*, 2005; Puglisi *et al.*, 2004). They are simple chlorophyll containing organism. They are accepted as simple because comparison of land plants and algae shows that algae do not have tissues which are organized into distinct organs. Algae are divided into two major groups: unicellular microalgae (*Microphytes*) and multicellular macroalgae (seaweed). The macroalgae can be identified in three major groups as green algae (*Chlorophyta*), brown algae (*Phaeophyta*), and red algae (*Rhodophyta*) (El Gamal, 2010).

The researches on algae for industrial and pharmaceutical purposes have revealed important chemical prototypes for the discovery of new agents, new sophisticated physical techniques, and new compounds with biomedical application. Besides, algae are promising organisms for providing both novel biologically active substances and essential compounds for human nutrition (Burja *et al.*, 2001; Mayer and Hamann, 2004). On the other hand, toxins produced by freshwater and marine algae represent an increasing hazard to water supplies, reservoirs, recreational beaches, as well as seafood contamination (Gehringer, 2004).

The nutritional value of marine algae has long been recognized in the Eastern culture; on the other hand, in the Western culture, the use of sea vegetables as nutrient is limited. Especially in the Far East countries like Japan, Korea, or China, sea vegetable has been preferred because the features of them such as containing vitamins and minerals. In many countries, the food industries consume a wide range of algae, which are well known to have high contents of fiber, minerals, vitamins, and different antioxidants. In the past few decades, the emphasis has moved from wild harvests to farming and controlled cultivation to produce valuable new products on a large scale (Nagaoka *et al.*, 2000).

Although pharmaceutical research on the algae products is very active, antigastrointestinal tract cancer activity from marine source studies have been few and mainly concerned with saccharides rather than the peptides or secondary metabolites. Even if there are a few saccharides that show antigastrointestinal tract cancer activity have been extracted from marine algae, they are still promising to be a rich source for human being to fight against cancer.

II. GASTROINTESTINAL TRACT CANCER

Gastrointestinal tract cancer is the malignant condition of the digestive tract, and it is the major health problem worldwide. Prognosis of the gastrointestinal tract cancer is grim against patients. Gastrointestinal cancer is often reported to result in metastatic conditions. Surgery is a curative option in 50% of colorectal cancers, but is less effective in gastric cancer, where the overall 5-year survival rate is less than 10%. Gastrointestinal cancer is divided into two main groups, depending on the organs which are affected from cancer. First group is called upper gastrointestinal tract cancer (Hasegawa *et al.*, 2003). This group includes esophagus and stomach cancer. Second group is lower gastrointestinal tract cancer and this group includes small intestine, appendix, colon/rectum (colorectal), and anus cancer.

III. GASTRIC CANCER

Gastric or stomach cancer is the second most frequent death cause of cancer, after lung cancer, around the world. Almost two-thirds of cases occur in Eastern Europe, South America, and Asia with 42% in China alone. In the United States, in 2009, an estimated 21,130 new cases of gastric cancer were diagnosed and were associated with 10,620 deaths (Jemal *et al.*, 2009), and it is one of the most common cancers in Europe ranking fifth after lung, prostate, colorectal, and bladder cancers in men and breast, colorectal, lung, and cancer of the corpus uteri in women. Sex-dependent ratio is (the male-to-female ratio in incidence rates) about 1.6:1 (Boyle and Ferlay, 2005).

There are geographic and ethnic differences in gastric cancer incidence in the world and in its trends for each population with time. The incidence patterns observed among immigrants change according to where they live. These factors indicate the close association of gastric cancer with modifiable factors such as diet. Substantial evidence from ecological, case–control, and cohort studies strongly suggest that the risk of cancer increases with a high intake of various traditional salt-preserved foods as well as salt per se and that this risk could be decreased with a high intake of fruit and vegetables (Kono and Hirohata, 1996). Also, there is some evidence that the intake of green tea and vitamin C is associated with the risk of gastric cancer. A recent report of a joint World Health Organization (WHO) and Food and Agriculture Organization (FAO) Expert Consultation concluded that salt-preserved food and salt probably increase the risk of gastric cancer, whereas fruit and vegetables probably decrease the risk (Petersen, 2003). Genetic factors are also important for the risk

of gastric cancer. Approximately 10% of cases show a genetic component. Other established nondietary factors include cigarette smoking (Anton-Culver *et al.*, 1993) and infection with the *Helicobacter pylori*. Although *H. pylori* lives in between the mucosal and the epithelial cells of the human stomach without adverse consequences, the presence of *H. pylori* is associated with an increased risk of gastric adenocarcinoma (Linz *et al.*, 2007).

The potential of the marine algae has been the driving force for the researchers to focus on the benefits of algae (Barros *et al.*, 2005; Puglisi *et al.*, 2004). The prevention of gastric cancer therefore represents one of the most important aspects of any cancer control strategy in around the world. Hence, radical scavenging compounds such as polysaccharides from seaweeds can be used indirectly to reduce cancer formation in human body.

Porphyran is sulfated polysaccharides from marine algae. Kwon and Nam purified polysaccharides from *Porphyra haitanesis* and evaluated its anticancer activity on AGS human adenocarcinoma cell (Kwon and Nam, 2006). It has been known that specific IGF-IR inhibition with neutralizing antibody, antagonistic peptide, or selective kinase inhibitor has activity against diverse tumor cell types and is one of the causes of antiproliferative/proapoptotic molecular induction (Li *et al.*, 2004; Saxena and Moorthy, 2007). In the study, the effect of IGF-I on porphyran-treated AGS cells was determined, and the result they declared that porphyran-induced apoptosis is involved in the IGF-IR-mediated signaling pathway in AGS gastric cancer cells. Moreover a porphyran purified from *Porphyra yezoensis* confirmed its apoptotic activity on AGS human adenocarcinoma cell line (Kwon and Nam, 2007). Porphyran that was isolated from red alga *P. yezoensis* also shows the apoptotic activity on AGS cell line. Further, Kwon and Nam declared that porphyran from different marine algae showed same apoptotic activity on AGS cell line by following mitochondrial pathway (Kwon and Nam, 2007).

Hwang *et al.* declared that polysaccharide extracted from *Capsosiphon fulvescens* inhibited alcohol-induced cell death and reduced the expressions of cyclooxygenase-2 (COX-2) and the inducible form of nitric oxide (iNOS), proteins related to ulcers (Hwang *et al.*, 2008). They proved that polysaccharide from marine algae also can be used as cancer protection agent.

Moreover, fucoidan is a fucan sulfate occurring in brown marine algae. Shibata *et al.* studied the inhibitory effect of *Cladosiphon* fucoidan on *H. pylori* adhesion to human stomach (Shibata *et al.*, 1999). Their researches proved that fucoidan inhibited bacterial binding to human gastric cell. It was also shown that this fucoidan blocks both Leb- and sulfatide-mediated attachment of *H. pylori* to gastric cells.

Hiroe *et al.* reported that glycoprotein which extracted from brown alga ''*Laminaria japonica* induces apoptosis on AGS adenocarcinoma

cells.'' They declared that glycoprotein extracted from *L. japonica* inhibited AGS cell growth by following multiple apoptotic (extinct and instinct) pathways. Treatment of glycolipid caused some changes in the Fas receptor pathway and the mitochondrial pathway (Go *et al.*, 2010).

Besides, acetone + methylane chloride and methanol extract of *Carpopeltis affinis*, *Sargassum tortile*, *Sargassum horneri*, *Sargassum fulvellum*, *Colpomenia sinuosa*, *Sargassum yezoense*, and *Sargassum hemiphyllum* inhibit the AGS cells' growth (Choi *et al.*, 2006). Besides methanol extract of marine algae *L. japonica*, *Porphyra tenera*, *Gelidium amansii*, and *Ecklonia cava* has inhibitory activity on AGS cell growth (Choi *et al.*, 2006). Their mechanism to inhibitions has not been clarified yet.

IV. COLORECTAL CANCER

The colon is a muscular organ and the last part of the digestive system in human, and the rectum is the final portion of the colon. Colorectal cancer is the third most common type worldwide (Boyle and Ferlay, 2005; Parkin, 2004) after lung and stomach cancer. Among them colon cancer is more frequent than rectal cancer. Especially in developed countries, the ratio of colon to rectum cancer cases can increase up to 2:1 or more. However, in nonindustrialized countries, rates are almost similar. On the other hand, comparison of the incidence rate of colon cancer in developed and underdeveloped countries shows that colorectal cancer is more common in industrialized countries. Also 50% of the colorectal cancer death has been seen in developed countries (Tyczynski *et al.*, 2003). It remains relatively uncommon in Africa and much of Asia. And rates of this cancer increase with industrialization and urbanization. It has been much more common in high income countries, but also now increasing in middle- and low-income countries too. It remains relatively higher in North America, Europe, and Australia rather than South America, Asia, and Africa (Parkin, 2004).

The development of colorectal cancer in humans involves genetic and environmental factors. A major environmental factor appears to be diet. Even if it has not been proved strongly, too much intake of red meat, processed meat, and alcohol drinks increases the risk of colorectal cancer (Chao *et al.*, 2005). The evidences are stronger for colon cancer than for rectum cancer. On the other hand, dietary calcium and vitamin D are inversely related to the incidence of colon cancer (Kwak and Chung, 2006). Another environmental risk factor for colorectal cancer is smoking. Smoking has consistently been positively associated with large colorectal adenomas (Giovannucci, 2001). There is strong evidence to suggest that alcohol and smoking have a greater relative effect together than alone. Another risk factor for colorectal cancer is genetic factors. Family history

is important for the risk of colorectal cancer like most of the cancer case. Especially the patients who are affected in early ages have family history in colorectal cancer (Strate and Syngal, 2005).

Natural products have yielded numerous effective anticancer drugs. In particular, many studies over the past few decades have focused on the benefits of algae. Algae are mainly composed of carbohydrates, proteins, and other minor components. They are used as food especially in Asian culture. This traditional food source appears to maintain good health by providing nutritional benefits and thus helping to combat diseases. Further, many compound extracted from seaweeds exhibit diverse biological activities, including effects on colorectal cancer.

Hiroe *et al.* reported that glycoprotein which extracted from brown alga ''*L. japonica* induces apoptosis on HT-29 human colon cancer cells.'' They declared that glycoprotein that extracted from *L. japonica* inhibited growth in a dose- and time-dependent manner (Go *et al.*, 2010). Also, the growth inhibition by glycolipid is associated with multiple apoptotic (extinct and instinct) pathways. Treatment of glycolipid caused some changes in the Fas signaling pathway and mitochondrial pathway. The Fas signaling pathway is a major apoptosis-related extinct signaling pathway. In this pathway mechanism, the Fas receptor signaling pathway is initiated by binding of the ligand on the cell surface, which then forms the DISC and activates caspase-8. Activation of caspase-8 initiates a cascade of caspases and leads to apoptotic cell death. Moreover, they also observed decreased levels of Bcl-2 expression and increased levels of Bad expression after *L. japonica* glycoprotein treatment. Bcl-2 and Bad are members of Bcl apoptotic protein family, and they play a vital role in mitochondrial apoptotic pathway (Go *et al.*, 2010).

Hosokawa *et al.* reported that fucoxanthin extracted from another brown algae *Undaria pinnatifida* induce apoptosis on Caco-2, HT-29, and DLD-1 cell lines. They declared ''Fucoxanthin reduced the viability of human colon cancer cell lines Caco-2, HT-29 and DLD-1 although the sensitivity for fucoxanthin among the three was different.'' Fucoxanthin decreased the level of the apoptosis-suppressing protein, Bcl-2. This indicates that the downregulation of Bcl-2 protein may contribute to fucoxanthin-induced apoptosis. It has a unique structure including an unusual allelic bond and 5,6-monoepoxide in its molecule. This structure may also give fucoxanthin an ability to regulate the redox signals and then facilitate the progression of apoptosis through Bcl-2 protein suppression and the caspase-dependent and -independent pathway (Hosokawa *et al.*, 2004).

Recently, only extract of brown algae shows activity against colon cancer cells. Mei *et al.* have published a study on that. In their study, they have collected brown algae, *Lethariella zahlbruckneri*, and extracted with methane and acetone. They declared that both extracts showed dose- and time-dependent antiproliferative activity on HT-29 cells (Ren *et al.*,

2009). Further, the apoptotic activities of extracts on HT-29 cells were evaluated. Finally, the study showed that acetone extract induced apoptosis via caspase-dependent and caspase-independent pathways (Ren *et al.*, 2009).

Besides, many active compounds have been characterized by researchers: sulfur-containing polybromoindoles were isolated from red alga, *Laurenda brongniartii* (El Gamal, 2010); aromatic sesquiterpenes, dimeric sesquiterpene of the cyclolaurane-type, sesquiterpene alcohol of bisabolene type were isolated from the organic extracts of *Laurencia microcladia* (Kladi *et al.*, 2007); terpenoid was isolated from tropical brown algae, *Styolpopdium zonale* (Dorta *et al.*, 2002); furoplocamioid, perfuroplocamioid, pirene, and tetrachlorinated cyclohexane from the red alga, *Plocumium carttilagineum* (Argandoña *et al.*, 2002); tetrahydro-β-carboline from the red alga, *Callophycus oppositifolius* (Ovenden *et al.*, 2011) which were active against HT-29 and SW480 cells.

V. CONCLUSIONS

While microalgae is the last ring of the food chain in all aquatic system, recently studies have provided that potential bioactive metabolites from macroalgae or sea vegetable can play a vital role in human health and nutrition. The designing of new functional foods and pharmaceuticals from marine algae makes them one of the most valuable marine sources. Many bioactive compounds have been purified from marine algae, but until now, most of the antigastrointestinal cancer activities of marine-derived extracts or compounds have not been observed *in vitro*. Therefore, further researches are needed in order to investigate their activity in human subjects.

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